Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 3-9, 11-20, 23, 24, and 40-44 are pending in the application, with claim 40 being the only independent claim. Claim 2 is sought to be canceled without prejudice to or disclaimer of the subject matter therein, canceled without prejudice to or disclaimer of the subject matter therein. Claims 1, 10, 21, 22, and 25-39 have been previously canceled without prejudice to or disclaimer of the subject matter therein, with claims 25-39 being drawn to non-elected invention. New claims 42 and 43 is sought to be added. Support for new claim 42 is found, for example, in the specification at paragraph [0080]. Support for new claim 43 is found, for example, in the specification at paragraph [0087]. Support for new claim 44 is found, for example, in the specification at paragraph [0075]. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objections to the Claims

Claims 40 and 3-6, 11, 13 and 41 were objected to because of the alleged informalities set forth in the Office Action, pages 2 and 3. Appropriate correction has been made to rectify all the alleged informalities. Applicant therefore respectfully request the objections be withdrawn. Applicants wish to address in detail the objection to the language in line 4 of claim 40 reading "optionally harvesting and re-suspending

the cultivated host cells." The Examiner asserts that this step cannot be optional because step b) requires "introducing the cell suspension" into a lysis reactor. However, as described in the specification at paragraphs [0071] to [0073], the term "cell suspension" is used for both resuspended cells after harvest and the fermentation broth which can be directly further processed without harvest and re-suspension of the cells. Thus, harvest and re-suspension of the cells is optional. To expedite prosecution, and without acquiescing to the rejection, Applicants have deleted "optionally harvesting and re-suspending the cultivated host cells this language." Amended claim 40 now precisely describes the invention and therefore renders the Examiner's rejection moot. In particular, step a) of amended claim 40 recites:

> a) cultivating host cells to produce the biomolecule of interest and forming a cell suspension of the cultivated host cells, wherein the cell suspension is a fermentation broth containing the cultivated host cells or a re-suspension of the cultivated host cells that are harvested from the fermentation broth.

Accordingly, step a) provides adequate antecedent basis for the phrase "the cell suspension" recited in step b). Applicants therefore respectfully request this objection be withdrawn.

As noted above, appropriate correction has been made to the claims in response to the remaining objections set forth by the Examiner. Applicants therefore respectfully request the objections to claims 40 and 3-6, 11, 13 and 41 be withdrawn.

Rejections under 35 U.S.C. § 112

Claims 2, 3, 5, 9, 11-20, 23, 24, 40 and 41 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. With regards to claim 40, the Examiner asserts

there is insufficient antecedent basis in claim 40 for "the lysis solution" (line 5), "the neutralizing solution [sic]" (line 12), and "the lysate" (line 17). Claim 40 has been amended so that "the lysis solution" (line 5) now reads "a lysis solution" and "the neutralization solution [sic]" (line 12) now reads "a neutralization solution." Step c) of claim 40 has been amended to recite "a lysate" so to provide adequate antecedent basis for "the lysate" (line 17). The Examiner also asserts that the language "top" when referring to the retention material is unclear. To expedite prosecution, and without acquiescing to the rejection, Applicants have deleted the language "on top . . . the retention material," thereby rendering the Examiner's rejection moot. Applicants therefore respectfully request the rejection of claim 40 be withdrawn.

With regard to claim 2, the Examiner asserts there is insufficient antecedent basis for the language "the lysate contains the biomolecule of interest." Claim 2 has been cancelled, rendering its rejection moot. Applicants therefore respectfully request the rejection of claim 2 be withdrawn.

With regard to claim 7, the Examiner asserts there is insufficient antecedent basis for the language "the mixture" and "the top" and it not clear what is encompassed by "top of the clarification reactor" as the clarification reactor is not designated with orientations. these terms. Claim 7 has been amended provide proper antecedent basis for "the mixture" (see claim 40) and "the top." Also with regard to claim 7, the Examiner asserts there is insufficient antecedent basis for the language "the lysate." Claim 40 has been amended to recite "a lysate," thereby providing proper antecedent basis to the language "the lysate" in claim 7. Applicants therefore respectfully request the rejection of claim 7 be withdrawn.

With regard to claim 11, the Examiner asserts there is insufficient antecedent basis for the language "the alkaline lysis solution." Claim 11 has been amended to recited "the lysis solution," which as antecedent basis in claim 40. Applicants therefore respectfully request the rejection of claim 11 be withdrawn.

With regard to claim 24, the Examiner asserts there is insufficient antecedent basis for the language "the host cells obtained in step a)". Claim 24 has been amended to recite that "the cell suspension obtained in step a) is cryo-pelleted." *See, e.g.,* paragraph [0069] of the specification. The language "the cell suspension" has proper antecedent basis in amended claim 40. Applicants therefore respectfully request the rejection of claim 24 be withdrawn.

With regard to claim 41, the Examiner asserts there is insufficient antecedent basis for the language "the surface of the retention layer" and asserts that the phrase "to reach" is unclear. To expedite prosecution, and without acquiescing to the rejection, Applicants have deleted the subject language and amended claim 41 to recite "extend to a surface of the retention layer." Applicants therefore respectfully request the rejection of claim 41 be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 2, 3, 5, 9, 11-20, 23, 24, 40 and 41 were rejected under 35 U.S.C. §102(e) as being anticipated over U.S. Patent Publication No. 2006-60106208 to Nochumson ("Nochumson"). Claim 2 is canceled, rendering its rejection moot.

Applicants respectfully traverse each of these rejections. Independent claim 40, at step b), recites "disintegrating the cultivated host cells by alkaline lysis in the lysis

reactor to produce a lysed cell solution, *wherein the lysis reactor contains a particulate material.*" The particulate material allows for mixing of the cell suspension and the lysis solution. Thus, the function of the lysis reactor is independent of whether and in which way the flows of the two solutions have been connected before they enter the lysis reactor. *See, e.g.,* paragraphs [0046] and [0080] of the specification.

In contrast, Nochumson does not disclose a lysis reactor that "*contains a particulate material,*" as claimed. Rather, Nochumson discloses an alkaline lysis process in which the means for providing mixing of the cells and the lysis solution for cell lysis involves an in-line static mixer and a lysis coil. *See* Figure 1 and paragraph [0055] of Nochumson. *See* also Background of the Invention section of the present application, at paragraph [0024], last sentence, which describes Nochumson's parent application U.S. Patent Publ. No. 2001/0034435. The Examiner asserts that Nochumson discloses a chromatographic step that uses reactors comprising particulate material; however, the chromotgraphic step does not correspond with the claimed lysis reactor, as the chromotgraphic step of Nochumson *follows* alkaline lysis. *See* Office Action, page 7. Nochumson does not disclose a lysis reactor that "*contains a particulate material,*" as claimed.

Since Nochumson lacks this claimed feature, it does not anticipate independent claim 40, or claims 2, 3, 5, 9, 11-20, 23, 24, and 41 which depend there from. Therefore, Applicants respectfully request that the rejections of these claims based on Nochumson be withdrawn.

Rejections under 35 U.S.C. §103

Claims 2, 3, 5, 9, 11-20, 23, 24, 40 and 41 were rejected under 35 U.S.C. §103(a) as being anticipated over the Nochumson reference in view of U.S. Patent No. 6,381,967 to Craig ("Craig"). Claims 2-9, 11-20, 23, 24, 40 and 41 were rejected under 37 U.S.C. §103(a) as being unpatentable over the Nochumson reference in view of U.S. Patent No. 5,561,064 to Marquet *et al.* ("Marquet") or U.S. Patent No. 5,783,686 to Gonzalez ("Gonzalez"). As noted above, Nochumson does not disclose a lysis reactor that "*contains a particulate material*," as claimed. The Examiner asserts that the art is replete with methods for clarification in which *lysates* are filtered through sinter plates or glass beads and cites Marquet and Gonzalez. *See* Office Action, pages 9 and 10. However, Craig, Marquet, and Gonzalez also do not disclose a *lysis* reactor that "*contains a particulate material*," as claimed. Marquet describes that lysis may be carried out in a dilute base or a base and detergent, or alternatively, lysis may be carried out by mechanical breakage using a French Press or a micro fluidizer. *See* col. 7, line 51 - col. 8, line 4 of Marquet. Marquet provides no description of alkaline lysis in the presence of particulate material. Gonzalez describes lysis by adding a solution of NaOH to the cells, and is also silent with regard to lysis in the presence of particulate material. *See* Col. 5., lines 10-12. Craig does not cure the deficiencies of Marquet and Gonzalez. Craig is directed to cryogenic freezing of liquids and makes no reference to cell lysis. The Examiner points out that KSR forecloses the argument that specific teaching, suggestion or motivation is required to support a finding obviousness. Notwithstanding, the Examiner has not shown a reason to combine the teachings of a clarification method using particulate material with an alkaline lysis method to arrive at a lysis reactor that

"*contains a particulate material*," as claimed. Neither the primary reference nor the secondary references teach the usefulness of employing a lysis reactor that contains a particulate material. Accordingly, the Examiner has not shown the claimed invention is obvious under KSR. Further, even assuming, *arguendo*, there exits a motivation to combine the filter systems of Marquet and Gonzalez with the process of Nochumson, it was surprisingly found that incorporating particulate material *in the lysis reactor* could achieve sufficient mixing and contacting for alkaline lysis. *See* paragraph [0046] of the present application. In sum, the Examiner has not set forth a *prima facie* case of obviousness.

Further, as noted in the Reply to the previous Office Action, filed December 21, 2007, the previously asserted reference U.S. Patent No. 6,660,472 to Santoro ("Santoro") is incompatible with an alkaline lysis method. Santoro mechanically lyses bacterial cells to release nucleic acids by vortexing the bacterial cells in a tube containing particulate material, such as glass beads. Mechanically lysing bacterial cells according to the method of Santoro will shear the genomic DNA present in the bacterial cells, thereby contaminating the biomolecule of interest with bacterial genomic DNA. Santoro therefore cannot be combined with the cited references to arrive at the presently claimed invention, which avoids mechanical shearing.

Accordingly, independent claim 40, and claims 2-9, 11-20, 23, 24, and 41, which depend therefrom, as well as new claims 42-44, which also depend from claim 40 and add further limitations to, are patentable at least for the reason noted above. Applicants respectfully request that the rejections be withdrawn and the claims allowed.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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